Cardiovascular Research and Medicine

Mini Review

Primary carnitine deficiency as a potential cause of short QT syndrome

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Abstract

Congenital forms of short QT syndrome (SQTS) are associated with QT interval abbreviation on the electrocardiogram, with atrial and ventricular arrhythmias and with an increased risk of sudden death. Whilst mutations in a number of ion channel and transporter genes have been identified in SQTS patients, often the underlying basis of the condition is not identified. This article briefly surveys evidence that primary carnitine deficiency (PCD), which arises from mutations in the *SLC22A5* gene, may be a cause of SQTS. Experimental evidence linking carnitine deficiency with accelerated repolarization is also discussed and a case made for the imperative for further work to understand underlying mechanisms of low-carnitine induced repolarization abbreviation.

Keywords: Carnitine; OCTN2; hERG; Primary carnitine deficiency; PCD; QT interval; SLC22A5; short QT syndrome; SQTS

A brief introduction to the short QT syndrome

Congenital short QT syndrome (SQTS) is a rare condition characterized by abbreviated rate-corrected QT (QTc) intervals on the electrocardiogram, often accompanied by tall T waves, and by poor rate adaptation of the QT interval [1-3]. It is associated with an increased incidence of atrial and ventricular arrhythmias and with an increased risk of sudden death [1-3]. European Society of Cardiology guidelines suggest a diagnosis of SQTS with a QTc interval of ≤ 340 ms [4]. QTc intervals exceeding this value but of ≤ 360 ms may be indicative of SQTS if there is evidence of one or more of: a familial history of SQTS or sudden death below age 40, survival from ventricular tachycardia (VT) or fibrillation (VF) in the absence of structural heart disease [4], or presence of a confirmed pathogenic mutation [4]. Thus far, eight distinct genetic SQTS variants have been identified that are associated with mutations to ion channels or transporters [3]. However, a relatively low proportion of patients who undergo genotyping (approximately 1 in 4 tested [5]) yield a mutation in an identified SQTS candidate gene, indicating that there is still much to discover about the underlying basis of QTc interval abbreviation in this condition. This brief article highlights why primary carnitine deficiency (PCD) should be evaluated as a potential cause of SQTS where examination of other genetic candidates proves negative.

An introduction to primary carnitine deficiency

Carnitine is a naturally occurring amino-acid obtained in the diet from meat and dairy produce and also produced endogenously in the liver and kidneys. L-carnitine is highly polar and is a critical metabolic cofactor, driving carnitine palmitoyltransferase I (CPTI), which is a rate-limiting step in the uptake into mitochondria and oxidation of long chain fatty acids (LCFAs) [6-10]. LCFAs are important energy sources in muscular tissue but cannot freely diffuse across the inner mitochondrial membrane [10]. Deficiency of carnitine therefore inhibits mitochondrial oxidation of LCFAs, leading to lipid accumulation in the cell cytosol. Active uptake of L-carnitine into the heart is controlled by the organic cation transporter 2 (OCTN2) encoded by the *SLC22A5* gene [11,12].

Primary carnitine deficiency (PCD; OMIM 212140) is a rare but potentially fatal genetic disorder characterised by low plasma carnitine levels and a deficiency of intracellular carnitine. It exists as an autosomal recessive disorder, due to mutations in the *SLC22A5* gene that encodes the high affinity, sodium-dependent carnitine transporter, OCTN2 (OMIM 603377), and is associated with metabolic crisis, hepatic encephalopathy and sudden death [10,13-15]. Carnitine levels in PCD are low intracellularly and plasma and high in urine (due to renal wasting). A cardiac manifestation of PCD is common (with one review reporting a > 60% exclusive cardiac manifestation [15]): patients develop a progressive cardiomyopathy, which is responsive to carnitine supplementation. Without diagnosis and treatment PCD patients develop lethal heart failure [10,15]. More than 100 disease causing mutations in *SLC22A5* have been identified [15], with variable correlation between genotype and phenotype, possibly due to a role for external influences in exacerbating or mitigating clinical phenotype [15,16].

Primary carnitine deficiency, arrhythmias and abbreviated repolarization

Cardiac arrhythmias have been described in both PCD patients and heterozygous carriers of *SLC22A5* mutations [10]. There is long-standing evidence that PCD leads to repolarization abnormalities. In 1981, T wave modification (tall, peaked T

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waves) was first reported in a young female PCD patient with cardiomyopathy [17], with subsequent studies reporting similar T wave changes in children with PCT and reversibility of these with carnitine supplementation [18-20]. Retrospective analysis of these studies showed simultaneous presence of tall T waves with abbreviated QT intervals [10]. Tall, peaked T waves together with abbreviated rate corrected (QTc) intervals are also characteristic of the congenital short QT syndrome (SQTS; [1,3]). In 2016, Roussel and colleagues reported patients from 2 unrelated families presenting with abbreviated QTc intervals in concert with *SLC22A5* mutations [21]. The first patient was a 21 month-old boy with low plasma free carnitine and a QTc of 309 ms, tall peaked T waves and low daytime QT dynamicity. He was found to have a W62X *SLC22A5* (premature stop codon) mutation inherited from his father and a R471C mutation from his mother. He also had mild dilated cardiomyopathy. The second patient was this boy's mother, who had undergone an episode of aborted sudden death due to ventricular fibrillation. She had an abbreviated QTc (340 ms) interval and increased T wave height. She had the same R471C mutation as transmitted to her son, with a complete deletion on the second allele of exon 2 of *SLC22A5* gene, and low plasma free carnitine [21]. Screening for mutations in known SQTS K^+ channel genes was negative. The third patient was from a different family and, again, had an abbreviated QTc interval (282 ms) and tall T waves. All three patients responded to carnitine supplementation. A further, recent report is of an 11 year old girl, originally identified at age 2 to have dilated cardiomyopathy possibly secondary to myocarditis, and treated pharmacologically with ACE inhibitors, diuretics, beta-blockers and digitalis [22]. Examined again at the age of 10, she showed severe left ventricular dilatation, bradycardia, and an abbreviated QTc interval (265 ms) with tall peaked T waves. Her blood carnitine was low and she had a heterozygous p.R289* truncation mutant in *SLC22A5*. A second variant was not found, but fibroblast analysis confirmed impaired carnitine transport. Carnitine supplementation improved her cardiomyopathy and increased her QTc interval [22]. It has been suggested that carnitine deficiency be suspected in situations of abbreviated QTc interval and/or unexplained cardiac arrhythmias [21]. This may be particularly the case where short QT intervals are concurrent with dilated cardiomyopathy [22].

Evidence for causality?

To understand better what the consequences of carnitine deficiency are for cardiac repolarization, Roussel and colleagues made a mouse model of carnitine deficiency [21]. For this, they used a drug called MET-88 (3-(2,2,2-trimethylhydrazinium) propionate; also known as mildronate or meldonium) which inhibits OCTN2 and the L-carnitine biosynthesis enzyme γ-butyrobetaine hydroxylase [23]. Treatment of mice for 28 days with MET-88 decreased plasma carnitine levels, induced cardiac hypertrophy and induced a significant increase in mitochondrial content of left ventricular myocytes [21]. ECG analysis did not show differences in basal heart rate, PR interval or QRS duration. However, there was a decrease in QT interval in MET-88 treated mice. 70% of treated mice also developed spontaneous sustained ventricular tachycardia and 50% developed VF. Cellular electrophysiology experiments were not performed to elucidate which ion channels/conductances were modified in the MET88 model [21]. However, the authors noted the ability of LCFA to regulate activities of different ion channels [21] and highlighted a possible role of the hERG/rapid delayed rectifier (I_{Kr}) current in mediating effects of carnitine deficiency as previous work had shown regulation of function of "hERG" (the channel underling I_{Kr}) by long-chain acyl-carnitines [24].

The need for further experimental investigation

The available information, summarised in the foregoing text, appears to be sufficient to indicate a causal relationship between PCD and QTc interval shortening. It is worth noting, however, that PCT may also present atypically with QTc prolongation [25] and this highlights a need to understand more deeply the relationship between OCTN2 dysfunction and cardiac repolarization mechanisms. Roussel and colleagues recommended that Class III antiarrhythmic drugs be employed to test the role of potassium currents in their mouse model of carnitine-deficiency linked QT interval shortening [21]. The changes to repolarization seen in the mouse PCD model certainly warrant further exploration at the cellular electrophysiology level, in order to understand the underlying basis of altered repolarization. It seems unlikely, however, that changes to I_{Kr} would be an explanation for their observations [21]. This is because the comparatively abbreviated mouse ventricular action potential differs markedly from that in humans and other animals that possess action potentials with a high plateau phase, and mouse ventricular myocytes rely on other currents than I_{Kr} to drive repolarization [26]. Thus, the primary effects on repolarization in the murine MET-88 induced carnitine deficiency model are far more likely to be attributable to effects on other ionic conductances and this merits experimental exploration. Furthermore, given the importance of I_{Kr} to human ventricular repolarization [27,28] and the ability of LCFA to modulate hERG channel function [24], it seems imperative also to develop an experimental model of PCD, perhaps using MET-88 [21], that uses a species with ventricular repolarization mechanisms closer to those in humans. Such work is likely to provide novel insights into pathophysiological modulation of ventricular repolarization and may highlight novel intervention point(s) for abbreviated repolarization disorders.

Conflicts of Interest

None

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